REMARKS

Reconsideration of the present application, as amended, is respectfully requested.

A. STATUS OF THE CLAIMS

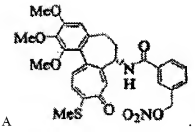
No claims are amended and no new matter is added.

B. SUMARY OF EXAMINER INTERVIEW

The undersigned wishes to thank the Examiner for his courtesy extended during the telephone interview conducted on August 9, 2011. It is believed that this amendment includes, where appropriate, the suggestions from the Examiner.

C. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

On page 4-8, claims 12-13 and 16-21 are rejected under 35 U.S.C. § 103(a), for allegedly being unpatentable over Kim et al. (WO 02/100824) in view of Patani et al. (Chem. Rev. (1996) 96:3147-3176). The Examiner maintained his position citing that the references teach enough evidence that fluorination would provide a similar biological activity that the substitution is obvious.



Compound A

Applicants respectfully traverse. Applicants respectfully would like to draw the Examiner's attention substitution of hydrogen with fluorine is not an obvious replacements by providing the secondary evidence to prove non-obviousness such as (1) physico-chemical effect of fluorination on the structure of compound of Formula (I); and (2) superior pharmacological activity of the compounds of the present invention containing fluorine ("F") compared the compounds in Kim et al. including reduced toxicity. These superior efficacy and toxicity profile is support by the data in the application and by the Study Result provided by the Inventors. To provide further evidence, a Declaration under 37 C.F.R. § 1.132 containing more detailed study report of toxicity profile will be submitted in due course following this response.

1. Difficulty of preparing compound of Formula (I) with multiple substituted phenyl group (e.g. B1)

Kim et al. synthesized compounds in the reference, having only one substituent (-CH_2ONO_2 or like) on phenyl ring in element such as B1, was prepared fairly straight forward by Kim et al. starting from commercially available chemicals. However, corresponding starting material for the compound of Formula (I) in the instant invention having multiple substitution on the phenyl moiety is nor readily available and, as provided in the application, the inventors designed and synthesized these compounds via novel synthetic route or with additional steps. Furthermore, having fluorine on the phenyl ring will change the chemical reactivities of the other substituents such as COOH to react with nucleophile to form intermediate for compound of Formula (I). Therefore, it is appreciated by the ordinary skills in the art that the design of synthetic route not analogous of Kim et al. or having more steps of chemical reactions is not a simple task but requiring in depth investigation. The ordinary skills in the art would easily recognize and appreciate that it is not obvious from Kim et al. to obtain the compounds of Formula (I) in the instant claims.

2. Change in Physico-Chemical properties

The -ONO2 substituent substituted in phenyl group may act as a hydrogen acceptor which makes hydrogen bonding with the amino acid of the target protein.

The halogen substituent of phenyl group influences the physicochemical property of the peripheral structure in which halogen is substituted due to the halogen's inductive effect (electron-withdrawing effect).

In other words, the bond strength, steric effect, conformation, electrostatic potential, dipole, pKa and lipophilicity variation of the compound molecules can be influenced as summarized in Tables 1-2.

[Table 1]: Physical property of C-H, and carbon-halogen bond

Element(X)	Electronegativity (Pauling)	Bond length (CH_2-X:Å)	van der Waals radius (Å)	Bond energy (kcal/mol)
H	2.1	1.09	1.20	98
F	4.0	1.39	1.35	112
Cl	3.0	1.77	1.80	81
Br	2.08	1.91	1.95	68
I	2.5	2.12	2.15	57

[Table 2]: pKa variation of compound due to halogen substitution

R		
H	10.00	4.60
o-F	8.81	3.20
m-F	9.28	3.50
p-F	9.95	4.53

Fluorine (F) substituted group, C-F, is a hydrogen bonding acceptor, and can make hydrogen bonding with -OH or –NH in the form such as C-F···HX (X=O, N). Regarding the binding pattern to proteins, it is generally known in the drug design research field that the binding pattern varies depending on presence and absence of halogen substitution in phenyl group and the effect also varies due to such variation in the binding pattern. In view of this, Applicants respectfully draw the Examiner's attention that, it is very likely that the compound substituted with -ONO2 or halogen alone will have **very distinct interaction with the target protein from the compound of the present invention in which -ONO2 and halogen are attached to the phenyl ring of B1**.

3. Change in Pharmacokinetic or Pharmacodynamic Profile

Further, substituting C-H of the compound with C-X (X = halogen0 can also affect kinetics

of metabolism and lipophilicity, for example, in vivo, to thus influence the pharmacokinetics (e.g., absorption, distribution, metabolism, secretion). This can influence drug absorption, tissue distribution, route of metabolism and rate of metabolism, which will also subsequently change the **efficacy and toxicity**.

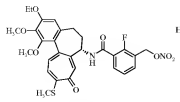
4. Superior pharmacological efficacy of the compounds of the present invention

The below confirms the superior pharmacological effects of compounds 8, 10, 12, 13 and 17 in which $-CH_2ONO_2$ and halogen (-F) are doubly substituted in phenyl ring, compared to compound 6 or 12 of Kim et al. in which $-CH_2ONO_2$ alone is substituted in phenyl ring.

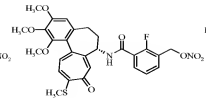
Table 3 provided below lists cytotoxicity (ED_{50}) of the compounds of the present invention in which -CH2ONO2 and halogen (-F) are doubly substituted in phenyl ring, against cancer cell lines based on Table 1 of the detailed description of the present invention.

[Table 3]: Cytotoxicity against carcinogenicity of the compounds of the present invention

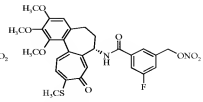
Examples	Cytotoxicity [ED_{50}:nM]				
	A549	SK-OV-3	SK-MEL-2	HCT15	MCF-7
Paclitaxel	0.2	1.5	0.1	0.1	0.9
Doxorubicin	13.0	47.0	16.0	25.0	50.0
Cholchicin	21.0	18.0	6.0	9.0	NT
Example 8	0.02	0.04	0.01	0.03	0.01
Example 10	0.28	0.23	0.12	0.39	0.09
Example 12	0.05	0.27	0.11	0.05	0.03
Example 13	0.13	0.18	0.04	0.11	0.02
Example 17	0.21	0.19	0.17	0.19	0.08



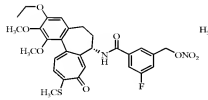
compound 8



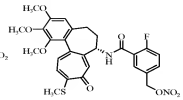
compound 10



compound 12



compound 13

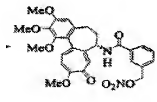


compound 17

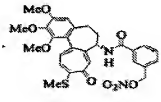
Meanwhile, Table 4 below lists cytotoxicity (ED_{50}) of compounds 6 and 12 of Kim et al. in which only -CH2ONO$_2$ is substituted in phenyl ring, against cancer cell lines based on Tables 2 and 3 of Kim et al.

[Table 4] Cytotoxicity against carcinogenicity of the compounds of Kim et al.

Examples	Cytotoxicity [ED_{50};nM]				
	A549	SK-OV-3	SK-MEL-2	HCT15	MCF-7
Paclitaxel	0.3	1.2	0.1	0.1	0.04
Compound 6	0.1	0.3	0.1	0.1	0.02
Compound 12	0.1	0.3	0.1	0.1	0.02



Compound 6



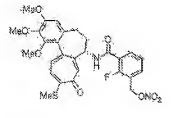
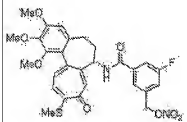
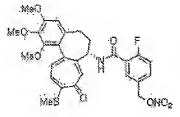
Compound 12

From Table 4, compounds 6 and 12 of Kim et al., in which -CH_2ONO_2 is mono substituted in phenyl ring, exhibit effect that is approximately two to four times higher than Paclitaxel.

However, the compounds of the present invention, in which -CH_2ONO_2 and halogen (-F) are both attached to the substituted phenyl ring, exhibit effect that is from several times to several

ten times higher than Paclitaxel, and particularly, ED50 with respect to MCF-7 is from 10 to 90 times greater than Paclitaxel.

[Table 5] Cytotoxicity to cancer cell lines for compounds 10, 12 and 17 of present invention, data from Table 1 on pages 139-140 of the present application.

	Cytotoxicity [ED_{50}: nM]				
Cell line	**A549**	**SK-OV-3**	**SK-MEL-2**	**HCT15**	**MCF-7**
Paclitaxel	**0.3**	**1.2**	**0.1**	**0.1**	**0.9**
Cpd. 10	0.28	0.23	0.12	0.39	0.09
	1 times	4 times	1 times	0.25 times	10 TIMES*
Cpd. 12	0.05	0.27	0.11	0.05	0.03
	6 TIMES*	4 times	1 times	2 TIMES*A	30 TIMES*
Cpd. 17	0.21	0.19	0.17	0.19	0.08
	1.5 times	6 TIMES*	1 times	0.5 times	11 TIMES*

A similar effect of fluoride on the biological activity can be also found among the compounds in the present application. Compounds 9 and 15 are fluorinated counterpart of compounds 3 and 7, respectively.

Note that the above-mentioned changes in physicochemical properties by the double substitution of $-CH_2ONO_2$ and halogen (-F) in phenyl ring can only be confirmed through actual

synthesis of the compounds and repeated test on the effects thereof. That is, the above-mentioned changes cannot be easily derived from the combination of Kim et al. and Patani et al. Considering the fact, introducing even one substituent to increase efficacy and toxicity of a compound, it is necessary to estimate changes in the physicochemical properties, and repeatedly introduce the substituent and verify the resultant efficacy.

5. Superior toxicity property of the compounds of the present invention

Compared to the compounds of Kim et al. in which only CH_2ONO_2 is mono substituted in phenyl ring, the compounds of the present invention in which -CH_2ONO_2 and halogen (-F) are doubly substituted in phenyl ring have superior efficacy as clearly confirmed by the toxicity property of these compounds as follows.

The inventors of the present invention noticed that Kim et al. conducted a test regarding oral administration toxicity of compound 6 from among the compounds in which -CH_2ONO_2 alone is singly substituted in phenyl ring. Accordingly, the inventors conducted tests and completed accurate comparison and evaluation of toxicity on the same route of oral administration of some of the compounds in which -CH_2ONO_2 and halogen (-F) are attached to the phenyl ring. Table 5 lists oral administering toxicity of the compounds of the present invention and Kim et al.

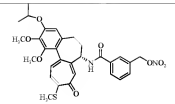
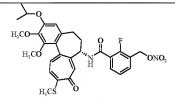
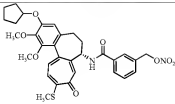
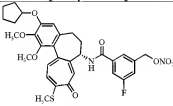
[Table 6] Oral administering toxicity of the compounds of the present invention and D1

	Compound	Oral administering toxicity(LD_{50})
Present invention	Example 8	1200mg/kg
	Example 12	1000mg/kg or above
Kim et al.	Compound 6	Approx. 10mg/kg (See Table 7 of Kim et al.)

Referring to the attached test result on oral administering toxicity (attached hereto) and Table 6, it is clear that the lethal dose 50 (LD_{50}) by one oral administration of Examples 8 (JAC-106) and 12 (JAC-067) of the present invention hovers around 1000 mg/kg. Also, the result significantly exceeds the oral administering toxicity (i.e., 10 mg/kg) of compound 6 of Table 7 (p. 49, Detailed Description of Kim et al.)

Such superior toxicity property of the present invention proves further view be anticipated from the combination of Kim et al. and Patani et al., and therefore, the present invention is not obvious in view of the cited inventions.

[Table 7] Compounds in the present application with H vs. F

	Cytotoxicity [ED_{50}; nM]				
Cell lines	**A549**	**SK-OV-3**	**SK-MEL-2**	**HCT15**	**MCF-7**
 [compound 3]	2.4	4.0	1.0	4.8	2.3
 [compound 9]	0.49	0.34	0.22	0.64	0.13
 [compound 7]	>50	>50	>50	>50	>50
 [compound 15]	30.2	>50	22.5	23.4	18.8

These results, in addition to the data in the present application support that the substitution of H with F is not an obvious variation of the compounds from the prior art.

In summary, considering the difficulties of preparing fluorinated derivatives, the

unexpected but significantly improved biological activities, and teaching away references available to those ordinary skilled in the art, the present invention and the instant claims are NOT OBVIOUS over the teachings by the cited references separately or in combination.

For all of the amendments and reasons above, reconsideration and withdrawal of this and future rejections is respectfully requested.

D. CLAIM REJECTIONS DUE TO DOUBLE PATENTING

On pages 20-22, all pending claims are rejected on the ground of non-statutory obviousness-type double patenting over claims 1-5 of US 7,119,229 in view of Patani et al. or over claims 1-4 of US 7,622,612.

-Non-Obvious over '229-

Applicants respectfully traverse on the ground of that the instant claimed subject matter is not obvious over the claims of the patent '229 based on the explanation provided above in section C.

-Improper Double-Patenting Rejection-

In addition, Applicants respectfully would like to draw the Examiner's attention that the double-patenting rejection over claims of US 7,622,612 is not proper because (1) there is no common ownership or inventorship; and (2) the subject matter in the patent '612 has US filing date of July 10, 2006 while those in the present invention was filed on June 23, 2004 as PCT/KR04/001518. Even though the patent '612 claims earlier priority date as a Continuation-In-Part of the patent '229 filed on May 27, 2002 as PCT/KR02/00996, the subject matter in the claims 1-4 of the patent '612 was not disclosed in the application of the patent '229. Thus, it is respectfully urged that the patent '612 be removed from the prior art.

For all of the amendments and reasons above, reconsideration and withdrawal of this and future rejections is respectfully requested.

E. FEES

This response is being filed timely with a petition for one (1) month extension of time and a Request for Continued Examination (RCE) with the required fees. The due date for one month of extension was September 10, 2011, a Saturday, and thus, this submission is considered to be timely. No further fee is believed to be required. If, on the other hand, it is determined that any fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

An early and favorable action on the merits is earnestly solicited.

F. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that each and every one of the matters raised by the Examiner have been addressed by the present amendment and that the present application is now in condition for allowance. However, Applicants reserve the right to respond to any outstanding issues which have not been addressed in this response. Furthermore, it is respectfully urged that the Examiner contact the undersigned with any question. An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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